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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/506,414	HUNG ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *22-27* is/are withdrawn from consideration.

5)☒ Claim(s) *14* is/are allowed.

6)☒ Claim(s) *1-13 and 15-21* is/are rejected.

7)☒ Claim(s) *15-21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Amendments

Applicant's response and amendments, filed October 4, 2007, to the prior Office Action is acknowledged. Applicant has withdrawn Claims 22-27 and amended Claims 1, 9-10, 12 and 14-15.

Applicant has elected the invention of Group I, Claims 1-14, with traverse, and the following restricted species: (a) human papilloma virus recited in Claim 2, (b) human papilloma virus type 16, as recited in Claims 4 and 11, and (c) a human papilloma virus, type 16, E6 and E7 genes, as recited in Claim 10.

The Applicant's argument that the Invention I composition of a substantially pure cell line of non-tumorigenic, immortalized human Schwann or Schwannoma cells and a method of making said cell lines contributes over the prior art is persuasive.

> 37 CFR 1.47(d) states: "If multiple products, processes of manufacture, or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT article 17(3)(a) and 1.476(c)."

Thus, Claims 15-21, as the first method of using the substantially pure cell line of non-tumorigenic, immortalized human Schwann or Schwannoma cells, are rejoined to Claims 1-14.

Claims 22-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-21 are under consideration.

Response to Amendment

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

The Hung declaration under 37 CFR 1.132 filed October 4, 2007 has been considered and is sufficient to overcome the rejection of claim 14 based upon i) the claimed human cell line was and still is the first and only available human immortalized Schwannoma cell line (¶1), ii) as far back as 1990, up until the present invention in 2002, the scientific community working in the field of Schwann cell and schwannoma cell research was either unmotivated to try to make immortalized human Schwann or schwannoma cells or unsuccessful in doing so (¶5), and iii) since the publication in 2002 of the inventor's manuscript describing the method of obtaining the

first ever immortalized human schwannoma cell line, which was the basis of the present application., the Assignee of this application, House Ear Institute, obtained material transfer agreements from 18 research groups to deliver the sample of the claimed cell line (HEI-193) for their research (¶7).

Priority

Applicant's claim for the benefit of the prior-filed U.S. Provisional Application 60/361,528, filed March 1, 2002 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the October 4, 2007 response will be addressed to the extent that they apply to current rejection(s).

Claim Objections

1. **Claims 1, 9, 12 and 15-21 are objected to because of the following informalities**:

With respect to claims 1, 9 and 12, the mutant NF2 gene is a genotypic trait, not a phenotypic trait.

With respect to claims 15-21, the claims are objected to as being dependent upon a rejected base claims 9 and 12, but would be allowable if rewritten as being commensurate in scope and dependent upon the allowable subject matter of claim 14.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit

On page 6, lines 7-8 of the Specification, the Applicants indicate that the preferred isolated HEI-193 human Schwannoma cell line actively expressing the E6 and E7 genes of human papilloma virus 16, wherein the immortalized cell line has a mutant NF2 gene and the phenotypic characteristics comprising rapid growth, antigen-positive for S100 has been deposited at ATCC under terms of the Budapest Treaty on July 11, 2002. The isolated HEI-193 human Schwannoma cell line was assigned the deposit number PTA-4544.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

Because the applicants have not fulfilled the declaration portion of the biological deposit rules, the examiner objects to this portion of the disclosure.

2. **Claim 14 is rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that biological material is required to practice the claimed invention. As such, the biological material must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the biological material.

The process disclosed in the specification does not appear to be repeatable. It is not clear that the invention will work with commonly available human Schwannoma cells, and it is not apparent if the isolated HEI-193 human Schwannoma cell line was assigned the deposit number PTA-4544 is both known and readily available to the public. It is noted that Applicants have deposited the cell line, but there is no indication in the specification as to public availability.

If a deposit is made under the terms of the Budapest Treaty, then a statement, affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, or someone empowered to make such a statement, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirements made herein.

Claim 14 would be allowable but for a statement, affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, or someone empowered to make such a statement, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent.

3. **Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph**, while being enabling for:

A) a method for producing an isolated HEI-193 human Schwannoma cell line actively expressing the E6 and E7 genes of human papilloma virus 16, deposited as ATCC Accession #PTA-4544, the method comprising the steps of:

a) providing a primary cell culture of human vestibular Schwannoma cells comprising a mutant neurofibromatosis 2 (NF2) gene, and

b) introducing a retroviral vector comprising human papillomavirus (HPV) E6 and E7 immortalizing genes into said cells, and

c) selecting for immortalized cells that express the exogenous immortalizing genes, have the mutant NF2 gene, and retain the phenotypic properties of Schwannoma cells, said phenotypic properties comprising rapid growth and antigen-positive for S100; and

B) an isolated HEI-193 human Schwannoma cell line actively expressing the E6 and E7 genes of human papilloma virus 16, deposited as ATCC Accession #PTA-4544, wherein the immortalized cell line has a mutant NF2 gene and the phenotypic characteristics comprising rapid growth, antigen-positive for S100 and,

C) a method for determining an effect of a pharmacological agent on the isolated HEI-193 human Schwannoma cell line actively expressing the E6 and E7 genes of human papilloma virus 16, deposited as ATCC Accession #PTA-4544, wherein the immortalized cell line has a

mutant NF2 gene and the phenotypic characteristics comprising rapid growth, antigen-positive for S100,

does not reasonably provide enablement for methods of immortalizing a genus of genetically diverse tumorigenic human Schwannoma cell types using replication-competent retrovirus, adenovirus and adeno-associated virus vectors encoding SV40 and adenoviral immortalizing genes, nor a genus of genetically diverse isolated tumorigenic human Schwannoma cell types, nor methods for determining an effect of a pharmacological agent on the genus of genetically diverse isolated tumorigenic human Schwannoma cell types.

This is a new rejection.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The breadth of the claim is exceptionally large for encompassing methods of making and using an enormous genus of Schwannoma cell types, each comprising distinctly different genetic and phenotypic properties than normal, non-transformed, non-tumorous cell.

The breadth of the claim is also large for encompassing distinctly different nucleic acid vectors, some of which are capable of inducing one or more genetic mutations as part of the step of introducing the immortalizing gene(s).

The inventive concept in the instant application is the isolation of a human vestibular Schwannoma cell line from a patient suffering neurofibromatosis, wherein the tumorigenic Schwannoma cells comprise a pre-existing mutation in the endogenous NF2 gene. The primary cell was transfected with a replication-incompetent retroviral vector encoding the HPV E6 and E7 immortalizing genes, and subsequently cultured and selected to establish an immortalized cell line, deposited as ATCC Accession #PTA-4544, wherein the immortalized cell line has a mutant NF2 gene and the phenotypic characteristics comprising rapid growth, antigen-positive for S100.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The Hung declaration states that "the claimed human cell line was and still is the first and only available human immortalized Schwannoma cell line" (¶1). Therefore, in light of the uniqueness of the claimed HEI-193 human Schwannoma cell line actively expressing the E6 and E7 genes of human papilloma virus 16, deposited as ATCC Accession #PTA-4544, either the inventive method of making an immortalized human Schwannoma cell line comprises a method step not known or used in the prior art so as to predictably yield the desired products, or the primary human Schwannoma cell from which the claimed product arose inherently possesses an essential and unpredictable property, not present in other primary human Schwannoma cells, that afforded successful immortalization by common methods known in the prior art.

The specification discloses the immortalization of human Schwannoma cells from a patient suffering from mutation in the NF2 gene. The primary human Schwannoma cell line was transfected with a retroviral pLXSN vector encoding the HPV E6 and E7 genes (pg 11, Immortalization). The specification does not disclose any additional method step not performed by the routineer.

In contrast to the routine method, the HEI-193 human Schwannoma cells are exceptionally abnormal, have diverse chromosomal complement, and manifest phenotypic traits that are not constant. The primary Schwannoma cells had already suffered genetic changes *in vivo* that transformed the cells from normal to neoplastic. Furthermore, once established *in vitro*

and transfected with HPV E6 and E7 genes, the HEI-193 cells began to acquire additional, novel phenotypic properties before and after the respective M1 senescence and M2 immortalization crises, such as increasing morphological heterogeneity, changes in cell proliferation rates, variation in S100 marker expression, and genomic instability such as changes in chromosome number and type (pages 13-15).

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The level of skill for the ordinary artisan in the field of cellular immortalization is considered high, as this technique has been practiced on a multitude of cell types obtained from a broad genus of vertebrate organisms. For example, Katakura et al (*of record) reviewed the knowledge in the art, wherein the art has long used nucleic acid vectors encoding SV40 large T antigen, HPV E6 and E7 proteins and adenovirus E1A proteins to immortalize mammalian cells. The art also teaches that normal, non-mutant Schwann cells may be isolated from mammalian tissues and immortalized *in vitro* (Peden et al, Annual N.Y. Acad. Sci 605: 286-293, 1990) by introducing an exogenous immortalizing gene into the non-mutant Schwann cell.

Katakura et al teaches that because immortalized human cells are never normal, they may express a tumorigenic phenotype to a varying degree (page 84, lines 1-3). Furthermore, retroviral vectors, e.g. pLXSN, integrate efficiently into the host genome, and that the level of immortalizing genes can be quite variable, depending on the integration site. This difference in immortalizing gene expression could alter cell proliferations and/or cell physiology (Katakura et al, pg 77, Gene Delivery, ¶1).

The characteristics of *in vitro* cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al (Leukemia and Lymphoma 9:1-25, 1993) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract).

Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Tian et al (Physiol Genomics, 17: 170-182, 2004) teach culture-induced artifact in macular RPE cells, wherein 950 genes are differentially expressed between native RPE and cultured RPE cells, and wherein 2080 genes are expressed in cultured RPE cells but are not expressed in native RPE cells (abstract, p.176). Similarly, Van Dyke et al (Cancer Genetics and Cytogenetics 241: 137-141, 2003) teach that random loss of chromosome 21 (monosomy 21) in patients with hematologic diseases is rare and should be confirmed by in situ hybridization (FISH), and that in most diagnosed cases the random loss of chromosome 21 is more likely due to artifact of culture of cells obtained from the patients (abstract, and pg 140, col. 1, last two paragraphs before acknowledgments). Zaslav et al (Amer J Medical Genetics 107: 174-176, 2002) teach that prenatal mosaicism for a deletion of chromosome 10 (q23) is rare, and that most diagnosed deleted (10q) mosaicism represents culture artifact, i.e. diagnosed individuals may have a deletion at this site when their isolated cells were grown in tissue culture or subjected to low folate conditions (abstract, and p. 175, first column, paragraph under Discussion). Kunkel et al (Neuro-oncology 3(2): 82-88, 2001) teach that teach that scatter factor/hepatocyte growth factor is overexpressed in most tumors examined, including glioblastomas, and that the lack of expression of scatter factor/hepatocyte growth factor in most cultured glioblastoma cells is not representative of the *in vivo* situation, and most likely represents a culture artifact (abstract).

The evidence presented thus clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, artifactual chromosome constitutions and antigen expression are expected and must be taken into account when experimenting with a given cell line.

While the method of immortalizing a mammalian cell is well-known in the art, the process of immortalization requires genetic change(s). Given the genomic instability observed in the instant cells, and the art-recognized unpredictability regarding the expression levels of immortalizing proteins encoded by a randomly integrating retroviral vector, one of ordinary skill in the art can reasonably conclude that the claimed immortalized product either possesses a

genetic feature acquired prior to or during the process of immortalization, the identity(ies) of which are both unknown and unpredictable.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

In conclusion, the specification fails to provide any guidance beyond the routine method known in the prior art so as to predictably transform primary human Schwannoma cells. In light of the uniqueness of the claimed HEI-193 human Schwannoma cell line actively expressing the E6 and E7 genes of human papilloma virus 16, deposited as ATCC Accession #PTA-4544 as being the first and only available human immortalized Schwannoma cell line" (Hung, ¶1), either the inventive method of making an immortalized human Schwannoma cell line comprises a method step not known or used in the prior art so as to predictably yield the desired products, or the primary human Schwannoma cell from which the claimed product arose inherently possesses an essential and unpredictable property, not present in other known primary human Schwannoma cells, that afforded successful immortalization by common methods known in the prior art.

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to achieve predictable levels of immortalizing gene(s) expression necessary to immortalize an enormous genus of primary human Schwannoma cells comprising distinctly different genetic mutations and possessing distinctly different phenotypes.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. **Claims 1-2, 6 and 9 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Peden et al (Annual N.Y. Acad. Sci 605: 286-293, 1990) and Rosenbaum et al (Neurobiology of Disease 5: 55-64, 1998).

This is a new rejection.

Peden et al teach primary rat Schwann cells immortalized with a plasmid encoding an exogenous SV40 T antigen oncogene, wherein the immortalized Schwann cells have retained the phenotypic properties comprising rapid growth (pg 291, Table 1) and antigen-positive for S100 (pg 290, line 4).

Peden et al do not teach immortalized human Schwannoma cells comprising NF2 mutations; however, at the time of the invention, Rosenbaum et al taught the isolation of NF2 Schwannoma cells from human patients, wherein said cells comprise the phenotypic characteristics of mutations in the NF2 gene (pg 58, Table 1), expressing the S100 marker (pg 59, Table 2) and increased growth rates (pg 59, col. 1). Rosenbaum et al taught a method of screening Schwannoma cell lines for NF2 mutations (pg 58, col. 1, Mutation and LOH Analysis). Rosenbaum et al taught that as the NF2 Schwannoma cells were passaged in culture, their relative purification from contaminating fibroblasts increased (pg 57, col. 2; pg 59, Table 2).

It would have been obvious to substitute the rat Schwann cells immortalized by the method taught by Peden et al with the human Schwannoma cells taught by Rosenbaum et al with a reasonable chance of success because both cells types are mammalian Schwann cells. The level of skill for the ordinary artisan in the field of cellular immortalization is considered high, as this technique has been long been practiced on a multitude of cell types obtained from a broad genus of vertebrate organisms, and there is no evidence of record for an inventive method step not known or practiced in the prior art. Absent evidence to the contrary, there is nothing non-obvious for substituting Schwann cells from a rodent with Schwann cells from a human. The simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

An artisan would be motivated to substitute the rat Schwann cells for human Schwannoma cells because Peden et al suggest that "[W]e are applying this approach to generate analogous cell lines from the peripheral nerves of other species such as mouse and human." "The ability to produce large numbers of human Schwann cells from nerve biopsy and to analyze their

biochemical properties would be of enormous value in identifying the cellular abnormalities that result in demyelinating disease. (pg 293, ¶2). An artisan would be further motivated to immortalize human NF2 schwannoma cells because Rosenbaum et al teach that "[A]lthough [primary cultures] NF2 Schwann cells still proliferate at higher passages, cell numbers could not be expanded infinitely. During long-term incubation it seems that NF2 Schwann cells change in morphology, grow extremely large, flatten, and contain multiple nuclei." (pg 59, col.2) The art recognizes the lack of an appropriate methodology to reliably examine the function of NF2 in the cells that manifest disease, namely Schwannoma cells. Rosenbaum et al suggest that the *in vitro* characterization of Schwannoma cells with disease-relevant genetic alterations may shed light directly on effects of these alterations and thus possibly provide crucial clues for understanding genotype–phenotype correlations in NF2. The ability to expand and compare NF2 and control Schwann cells *in vitro* can provide a model with the authentic cell type and genotype for investigation of the pathogenesis of NF2.

Thus, the invention as a whole is *prima facie* obvious.

Applicant's Arguments

Applicant argues that:

a) Peden et al do not teach or suggest using human Schwannoma cells having a pre-existing NF2 mutation; and

b) no one was even motivated to try to immortalize human tumorigenic Schwannoma cells (pg 9, last sentence).

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), in response to applicant's argument that the references do not provide that a specific teaching, suggestion, or motivation to support a finding of obviousness, *KSR* forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, USPQ2d, slip op. at 20 (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR International Co. v. Teleflex Inc. (KSR)*, 82 USPQ2sd at 1396) (available at www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

The substantive issue is that methods of immortalizing mammalian cells, including human cells, have long been known in the art and there is no evidence of record for an inventive method step not known or practiced in the prior art. Furthermore, Peden et al teach the intentions of applying the method of immortalization to Schwann cells obtained from humans. Applicant has provided no evidence as to why the existence of an NF2 mutation in a human Schwannoma cell would preclude the artisan from applying known methods to immortalize mammalian cells to Schwann cells obtained from humans.

With respect to b), the declaration of Hung states that "the scientific community working in the field of Schwann cell and schwannoma cell research was either unmotivated to try to make immortalized human Schwann or schwannoma cells **or unsuccessful in doing so**" (¶5) indicating that methods for producing immortalized human Schwannoma cells were in practice before the invention. While the attempts may have been unsuccessful, artisans were motivated to try to immortalize human tumorigenic Schwannoma cells.

5. **Claims 3-5, 7-8 and 10-13 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Peden et al (Annual N.Y. Acad. Sci 605: 286-293, 1990) and Rosenbaum et al (Neurobiology of Disease 5: 55-64, 1998) as applied to claims 1-2, 6 and 9 above, and in further view of Roque et al (Exp. Eye Res. 64: 519-527, 1997); Schlegal (U.S. Patent No. 5,376,542) and Katakura et al (1998, *of record), as evidenced by Li et al (Cancer Biotherapy & Radiopharm. 18(5): 829-840, 2003).

This is a new rejection.

The prior cited art does not teach the immortalizing polynucleotide to be from human papilloma virus. However, at the time of the invention, Roque et al summarized the general knowledge in the art that recombinant HPV type 16 viruses encoding the E6 and E7 proteins have long been used in the art to immortalize mammalian cell types, including human keratinocytes, fibroblasts and mammary epithelial cells (pg 526, col. 1, ¶2). Roque et al teach the use of recombinant, replication defective retroviral vector encoding the HPV-16 E6 and E7 proteins to immortalize rat Muller cells, a type of neural glial cell, from a mixed retinal cell culture (pg 520), wherein the art recognizes retroviral vectors integrate into the host nuclear

genome (see, for example, Li et al, pg 831, col. 2, Infection Efficiency and Integration, and Figure 1, as it relates to the pLXSN recombinant retroviral vector).

Roque et al do not teach the E6 and E7 genes to be obtained from HPV-18, 31, 33 or 35 viral types. However, at the time of the invention, Schlegal disclosed that [retroviral] vectors containing HPV-16, 18, 31, 33 or 35 E6 and E7 genes may be used to immortalize cells (col. 5, lines 63-64; col. 6, lines 38-39). Neither Roque et al nor Schlegal et al teach the immortalizing polynucleotide to be from adenovirus. However, at the time of the invention, Katakura et al reviewed the knowledge in the art, wherein the art has long used recombinant viral vectors encoding SV40 large T antigen, HPV E6 and E7 proteins and adenovirus E1A proteins to immortalize mammalian cells.

It would have been obvious to substitute the SV40 T antigen immortalizing gene of Peden et al to be either the HPV-16 E6 and E7 proteins or adenovirus E1A protein as taught by Rogue et al, Schlegal et al and Katakura et al with a reasonable expectation of success because the art has long recognized these proteins having immortalizing properties "to generate cell lines from cell types that are not abundant or are difficult to obtain in pure form in primary culture, are in short supply as human cells, and/or have brief lifetimes in culture." (Katakura, pg 70) Absent evidence to the contrary, nothing non-obvious is seen with replacing one immortalizing gene with another immortalizing gene because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute one immortalizing gene for another as part of normal experimental optimization of conditions, e.g. so as to fulfill the size constraint needs of the immortalizing vector.

It also would have been obvious to substitute the immortalizing gene of Peden et al or Roque et al to be either the HPV-31, 33 or 35 E6 and E7 proteins as taught by Schlegal et al with a reasonable expectation of success because the art has long recognized these proteins having immortalizing properties. Absent evidence to the contrary, nothing non-obvious is seen with replacing the E6 and E7 immortalizing genes from any of the recited HPV types because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention and the art recognizes that the E6/E7

genes from each of the viral subtypes has immortalizing properties. An artisan would be motivated to substitute one immortalizing gene for another as part of normal experimental optimization of conditions, e.g. so as to fulfill the size constraints of the nucleic acid vector.

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. The specification does not disclose any additional method step or element not performed or used by the routineer prior to the invention.

Thus, the invention as a whole is *prima facie* obvious.

Applicant's Arguments

Applicant argues that Roque et al, Schlegal et al and Katakura et al do not cure the deficiencies of Peden et al and Rosenbaum et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The response to the arguments of Peden et al and Rosenbaum et al discussed above are incorporated herein. Applicant does not argue the non-obviousness of the subject matter for which Roque et al, Schlegal et al and Katakura et al teach.

6. **Claims 15-21 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Peden et al (Annual N.Y. Acad. Sci 605: 286-293, 1990), Rosenbaum et al (Neurobiology of Disease 5: 55-64, 1998), Roque et al (Exp. Eye Res. 64: 519-527, 1997), Schlegal (U.S. Patent No. 5,376,542) and Katakura et al (1998, *of record), as evidenced by Li et al (Cancer Biotherapy & Radiopharm. 18(5): 829-840, 2003) as applied to claims 1-13 above, and in further view of Einheber et al (Journal of Cell Biology 129(2): 443-458, 1995), Bonetti et al (J. Neuropathol. Exp. Neurol. 59(1): 74-84, 2000) and Steele et al (Carcinogenesis 21(1): 63-67, 2000).

This is a new rejection.

The prior cited art does not teach a method using the immortalized cells for determining the effect of a pharmacological agent on human Schwann or Schwannoma cells.

However, at the time of the invention, Einheber et al taught the evaluation of numerous phenotypic characteristics in primary rat Schwann cells in response to the administration of

TGFβ-1, alone or in combination, with the chemical drug forskolin, such as expression of Schwann cell markers, myelination of neurons in co-culture, changes in basal lamina formation, proliferation and expression growth factor receptors (see entire document). TGFβ-1 is well known in the art to be a growth factor and to have profound effects on Schwann cell proliferation and differentiation that are context dependent, such as increasing the expression of NCAM cell adhesion molecule and the SCIP transcription factor (page 444, column 2, lines 38-62). Forskolin is known in the art to elevate cyclic AMP levels, and depending on the concentration, may increase Schwann cell proliferation or stimulate Schwann cell differentiation and myelination. Forskolin also induces expression of the SCIP transcription factor, which in turn inhibits expression of the p75 nerve growth factor receptor and the myelin protein P0 (page 444). Similarly, Bonetti et al taught the evaluation of numerous phenotypic effects when treating primary human Schwann and Schwannoma cells with the TNFα cytokine, alone or in combination with, the chemical drug acetylsalicylic acid, such as changes in cellular gene expression such as Schwann cell transcription factors, signaling molecule, growth factor, growth factor receptor, myelination of neurons in co-culture, proliferation, expression of growth factor receptors, and apoptotic events (see entire document). Likewise, Steele et al taught several *in vitro* bioassays, including inhibiting carcinogen binding to DNA, the generation of free radicals, anchorage-independent growth inhibition, focus formation inhibition, mammary organ culture alveolar nodule inhibition and induction of cellular enzymes-an activity that potentially identifies chemopreventative agents to assess possible cancer chemoprotective effects due to exposure of black and green tea extracts, and the chemicals therein as applied to several human and murine cell types (see entire document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cell types as taught by Einheber et al, Bonetti et al and Steele et al with the immortalized human Schwannoma cells of the prior cited art with a reasonable chance of success because Einheber et al and Bonetti et al demonstrate that Schwann cells may be used *in vitro* to assay diverse phenotypic responses, such as viability, morphology, differentiation, proliferation and gene expression, upon exposure to an exogenous compound. Furthermore, the Applicant's own admission that the numerous assays and techniques to measure genotoxicity, DNA adduct formation, mutagenicity, cell transformation and/or cytotoxicity, cell growth and

colony formation are standard techniques well known in the art (page 8, lines 25-29, page 9, lines 9 and 20). An artisan would be motivated to use the immortalized human Schwannoma cells of the instant application in diverse pharmacology assays because the invention enables others to perform studies regarding Schwann cell biology and development, such as studying gene-gene interactions, mechanisms of mutagenesis and tumorigenesis of Schwannoma cells, and assess possible therapeutic interventions, such as drugs that reduce the growth rate of the tumors, that would not have been possible using primary, mortal Schwann cell cultures or non-Schwann cell types.

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. The specification does not disclose any additional method step or element not performed or used by the routineer prior to the invention.

Thus, the invention as a whole is *prima facie* obvious.

Applicant's Arguments

Applicant argues that Einheber et al, Bonetti et al and Steele et al do not cure the deficiencies of Peden et al and Rosenbaum et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The response to the arguments of Peden et al and Rosenbaum et al discussed above are incorporated herein. Applicant does not argue the non-obviousness of the subject matter for which Einheber et al, Bonetti et al and Steele et al teach.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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